Biomedical Computing in the Environmental Health Sciences at Mississippi State University: Simulation of Toxicant Interaction With Target Enzymes and Enzymes of Metabolism

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Biomedical computing efforts at Mississippi State University in the environmental health sciences are targeted at simulation of dynamic biological processes involved in the adverse consequences of environmental toxicant action on human health. Two important current investigations are concentrated on the simulation of toxicant interactions in biological systems, either at the molecular level or at the organ level. The toxicants of primary interest at present are the widely used organophosphate insecticides that are neurotoxic, inhibiting the critical nervous system enzyme acetylcholinesterase, following metabolic activation by cytochromes P450. In a computational chemistry project we are building a computational model of the acetylcholinesterase molecule based on the highest resolution x-ray crystal structure currently available. The simulation has involved placing the 8,339 atoms of the protein in a box of 25,000 water molecules and generating the lowest energy conformation of the protein. Additionally, the conformations of some common organophosphate structures were modeled. Currently, the organophosphates are being docked into the acetylcholinesterase active site. Next, we will calculate binding affinities, and, by studying the mechanism of reaction, we will also derive rates of phosphorylation. The ultimate goal is to be able to predict association constants for a variety of anticholinesterase compounds. The second project is designed to model the bioactivation of organophosphate insecticides spatially in the acinus of the liver. Cells lining the sinusoid in the acinus possess varying levels of P450's, suggesting that bioactivation would occur at different rates at different places within the acinus. Initial modeling efforts will consider sinusoid and cell layer cross sectional areas, diffusion and convection of substrate and product within the sinusoid, exchange of substrate and product diffusion across cell membranes, blood flow, and kinetics of product formation. The model would be in the form of a system of nonlinear parabolic partial differential equations and ordinary differential equations. Experimental data will be used to calibrate the model and attempt to predict future experimental results. The current plan for the numerical treatment of the model is to use a semidescretization in space methods based on the Legendre Gaussian nodes and then use standard implicit multistep stiff solvers to deal with the resulting temporal ordinary differential equations. The resultant model will be expanded to include additional metabolic pathways. The model will have utility in predicting the hepatic metabolism of a variety of compounds for different ages or different physiological states.

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